THE HARTWELL FOUNDATION

2009 Individual Biomedical Research Award

Review of Proposed Research

Investigator: **Asim Beg, Ph.D.**
Assistant Professor
Department of Pharmacology

Institution: **The University of Michigan**

Proposal: **Activity-dependent Remodeling of the Corticospinal Motor System**

Dr. Beg proposes to develop mouse models that mimic the anatomical and behavioral defects observed in hemiplegic cerebral palsy (HCP), an acquired disorder that appears in children before the age of 3 with an incidence of 1 per every 500 live births. HCP impairs control and coordination of body movement (arm and leg) on one side of the body. In most cases, muscles feel tight, rigid and seem permanently contracted, with reduced growth. Cerebral palsy is generally believed to be caused by damage or trauma to the brain before it has completed development. The areas of the brain most affected are associated with the *central motor system*: nerve pathways originating in the brain cortex or brainstem that descend down the spinal cord to control skeletal muscle. The cause of the condition is associated with numerous risk factors for pregnancy, delivery and neonatal care; but in 20-50% of cases the cause remains unknown. There is no known cure, but early diagnosis and treatment (e.g., constraint-induced movement therapy) often can improve a child's long-term capabilities. Today, strategies for prevention and treatment of cerebral palsy target the biological mechanisms, where the key to achievement will be in finally developing appropriate animal models for long-term longitudinal studies. Understanding developmental mechanisms that ensure strong and specific corticospinal tract connections will offer insight required for preventing the progressive neural circuit changes in babies following brain trauma, as well as direction for repair of aberrant neural circuits and restoration of normal motor control in those children already affected. For example, Dr. Beg has recently characterized a mouse line in which the gene for α2-chimaerin protein was gene-trapped, leading to impairment in guidance of corticospinal tract axons, as well as other neurons that depend on this signaling. The animals had a curious form of locomotion in which the hind limbs synchronously hop rather than alternate. He seeks to use these mutant mice as a platform to investigate how activity-dependent interactions may be responsible for this debilitating disorder. However, the motor cortex behavioral changes that occur in the α2-chimaerin mutants could reflect circuit changes at any level in the central motor system. A major advance for studying motor behaviors would be to produce the gene knockout only in corticospinal tract neurons. To determine the effects of eliminating or reducing the level of motor cortex activity on normal development, where elimination of a key guidance signal results in bilaterally-organized corticospinal motor systems, he proposes using α2-chimaerin conditional knock-out mice. If successful, Dr. Beg will create the desired animal model with anatomical and behavioral defects observed in hemiplegic cerebral palsy required to study the disease.